The future of murine sepsis and trauma research models

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ABSTRACT

Recent comparisons of the murine and human transcriptome in health and disease have called into question the appropriateness of the use of murine models for human sepsis and trauma research. More specifically, researchers have debated the suitability of mouse models of severe inflammation that is intended for eventual translation to human patients. This mini-review outlines this recent research, as well as specifically defines the arguments for and against murine models of sepsis and trauma research based on these transcriptional studies. In addition, we review newer advancements in murine models of infection and injury and define what we envision as an evolving but viable future for murine studies of sepsis and trauma. J. Leukoc. Biol. 98: 000–000; 2015.

Introduction

Sepsis and traumatic injury are 2 major unresolved issues in the field of critical illness, as both continue to be major causes of human morbidity and mortality. For example, sepsis is an increasingly significant problem throughout the world, and infections remain 1 of the top causes of poor outcomes [1, 2]. Severe sepsis and septic shock have estimated in-hospital mortalities of 29–40% and >50%, respectively [3-5]. Even with improvements in patient outcomes as a result of efforts to standardize initial patient care [6, 7], the total number of deaths as a result of sepsis is growing because of its increasing incidence [8]. Trauma is no different; severe traumatic injury is responsible for a major percentage of deaths worldwide [9]. Although advances in critical care have substantially improved the initial mortality associated with sepsis and trauma, many patients who survive the initial injury succumb from complications [10-14]. To date, immune modulation therapy and pharmacotherapeutic agents have proven disappointing in regards to modifying any human outcome, despite promising results from preclinical studies [15]. Much of this preclinical work was done in rodent models [15]. Thus, despite decades of promising preclinical and clinical investigations that have elucidated individual aspects of the complex pathophysiology present in infection and injury, our understanding of these entities remains incomplete, and few therapies have successfully improved outcome in these critically ill patients [16-18]. It is clear from this that the best methodology to study severe infection or injury has yet to be determined and is in evolution.

With over 2 decades of, at worst, failure and, at best, modest improvement in translational research in sepsis and trauma, many have questioned the animal model and the reductionist approach used to address these 2 syndromes. More specifically, the question being asked is if the millions of dollars invested in rodent sepsis and trauma research have literally wasted investigative opportunities and funding [19]. Simultaneously, many have turned to large human and murine datasets by use of a systems approach to compare transcriptional regulation in humans and mice and in some cases, compare them with clinical outcomes. In this era of big data [20-24], relatively recent projects have focused on a comparison of the transcriptional regulation between mouse and humans. For example, the Mouse ENCODE Consortium mapped transcription, DNsase I hypersensitivity, transcription-factor binding, chromatin modifications, and replication domains throughout the mouse genome and compared the results with healthy humans [25]. Shay et al. [26] and the Immunologic Genome Consortium examined the murine and human transcriptional response from multiple hematopoietic cell populations in health. The “Inflammation and Host Response to Injury” GG conducted a 10 yr prospective, multi-institutional observational study in human and murine trauma and burns, with the primary aims of describing the epidemiology, proteomic, and leukocyte genomic responses [27, 28]. All of these programs have provided a unique opportunity to compare systematically large swaths of genomic data in healthy patients and mice, as well as after trauma or burns.

ARGUMENTS AGAINST MURINE MODELS

At this time, no interventional biologic therapies proven successful in mouse models of sepsis or trauma have been
ARGUMENTS IN FAVOR OF MURINE MODELS

Although few have refuted the validity of the work by Seok et al. [29], many have disputed its conclusions and interpretations [19, 30, 32]. After publication of this article, there has been a subsequent, robust discussion of the data and its analyses. Some of the furor was undoubtedly directed against the discussion and its tone. In addition, a revised analysis of the same human and murine injury dataset came to completely opposite conclusions. Takao and Miyakawa [30], in a more recent publication, reanalyzed the data of Seok et al. [29] and came to the conclusion that, “...gene patterns in mouse models closely recapitulate those in human inflammatory conditions and strongly argue for the utility of mice as animal models of human disorders” [30]. However, the authors limited their analyses not to the entire human and mouse orthologous genome but to 2300 homologous genes whose expression changed after trauma, burns, or endotoxin in mice and humans. Osuchowski et al. [19] went beyond the genome and argued that murine models have recapitulated the human disease at a number of physiologic and organ system levels [19, 29, 30]. These authors have claimed that it is too early to reject murine models when there is such a long history of demonstrating similar physiologic and immunologic responses to human inflammation. There is undoubtedly truth to these conclusions, but one view of all of the data would suggest that mice and humans accomplish the same immunologic responses and functions through the expression of overlapping but different patterns of genes. Such data would coincide with the conclusions reached by the Mouse ENCODE Consortium [25] but differ from the conclusions of Shay et al. [26]. Such a conclusion could also explain why individual targeted therapies that are successful in mice may not be equally effective in humans.

There are, however, a number of additional issues that complicate the comparison of murine with human injury models that are more dependent on the differences in the models and their management than the disparate species response. Most murine models have used a polymicrobial sepsis produced by CLP, or trauma produced by hemorrhagic shock and surgical injury [39, 40]. Although these models have been well standardized and are accepted by the scientific community, they are generally assumed to poorly recapitulate human sepsis,
Mismatching the temporal
Genome-to-protein gap
Transcription does not equal translation.

Compartmentalization of the
Analysis of responses in a
Model and severity mismatch
Previously accepted models of murine sepsis and trauma mildly imitate the severe and
peritoneal sepsis in the same aged mouse strain with fecal
slurry [25, 29, 41]. Although both are models of polymicrobial
Total circulating leukocyte
Age
Mortality is increased significantly in the elderly in sepsis and trauma, and the incidence is
increased in the former as well. Typical murine studies use animals that are the age
equivalent of an adolescent human and thus, cannot reflect the majority of sepsis
patients nor those at the greatest risk for poor outcomes after trauma [32–34].

Strain
Single mouse strains cannot be expected to represent the entire genetic diversity of the
entire mouse and human population.
Sex
Single mouse sex studies cannot represent human mixed sex-disease processes or datasets.

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Previously accepted models of murine sepsis and trauma mildly imitate the severe and
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Analysis of responses in a
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Blood and circulating leukocytes are used for murine-human comparisons as a result of
our ability to obtain human blood samples with relative ease. However, inflammation is
a systemic phenomenon that affects virtually every organ, and the interspecies
comparison of these other organs (i.e., liver) after injury or infection of the host
illustrates that they can be quite similar.
Compartmentalization of the
immune-inflammatory
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Changes in the circulation are not tantamount to the changes that occur in other organs
and local tissues.
Genome-to-protein gap
Mismatching the temporal
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Transcription does not equal translation.
Twenty-four hours in a mouse is not the equivalent of 24 h in a human being [32].

**TABLE 1. Partial list of limitations of current murine models used to conduct sepsis and trauma research**

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*Adapted from Osuchowski et al. [19].

Trauma, and their management. In fact, with the use of the same genomic analyses performed by the GG and Mouse ENCODE Consortium, we compared the genomic responses among two models of sepsis, a CLP, and the intraperitoneal injection of cecal slurry [25, 29, 41]. Although both are models of polymicrobial peritoneal sepsis in the same aged mouse strain with fecal flora, the genomic responses differed significantly [41]. In actuality, the differences in genome-wide transcription between the two models of sepsis were greater than a comparison of the CLP (polymicrobial sepsis) with a much more severe, multicompartmental trauma model [41] (unpublished data). These findings are markedly different than the findings of Seok et al. [29], who failed to see any relationship between leukocyte gene-expression patterns from burned mice and mice receiving hemorrhagic shock and surgical injury [29]. In fact, the disparities of these findings with that of Seok et al. [29] argue that the choice of animal models and their timing are essential criteria for comparing results among different murine models and with humans. Although our work indicates a much greater similarity in the total leukocyte genomic response between mouse models of infectious and noninfectious inflammation, it is essential to heed the advice of Osuchowski et al. [19]. These authors emphasized the need for all investigators in the future to consider the relevance of their models to human disease before embarking on sepsis and trauma research in mice (Table 1) [19].

**REVISION, RATHER THAN REJECTION, OF MURINE MODELS**

“Strive for progress, not perfection!” — unknown author

Most advances in human medical science have not been made from direct human experimentation. In fact, the evaluation of new therapeutic advances directly in human subjects is a clear violation of the ethical guidelines embraced by the Nuremberg code and the Declaration of Helsinki, which states that animal testing is a required prerequisite before human testing. There have been multiple examples of how past mouse-to-human translational work has successfully advanced the field of inflammation research and provided benefit to humankind [19]. However, much of the trepidation surrounding the use of murine models for sepsis and trauma research has been a result of our inability to identify a single therapeutic intervention that has translated into a benefit for patients. Some of this can be blamed on an inappropriate understanding of the complexity of severe inflammation in the mammalian host and an over-reliance on reductionist approaches. A modification of Koch’s postulates has often been proposed for the identification of an individual mediator or therapeutic approach for the treatment of sepsis or severe trauma. This has led to an experimental approach based on the linear thinking of the following: that 1) “mediator A produces disease when administered to a healthy animal”; 2) “mediator A is produced in the disease, but not in healthy individuals”; and 3) “preventing mediator A production blocks the expression of the disease.” Based on this reasoning, a multitude of individual mediators has been explored as potential targets for sepsis or trauma interventions. Although such reductionist approaches to experimentation have been absolutely vital to the scientific process and to scientific progress, sepsis and trauma are not “simple and clean” monogenic diseases. Rather, trauma and sepsis are polygenic phenotypes with multiple simultaneous aberrations [27]. This "storm" (whether cytokine or genomic [27]) that occurs with severe infection or injury affects every aspect of mammalian biology—multiple molecules, genes, cells, tissues, compartments, and
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models of murine trauma only induce a transient period of
patients under the intensivist
middle-/high-school children in their ICUs. The answer will be
When experiments moved from in vitro studies to animal models,
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for human patients because of aggressive interventional support
severe human infection; a greater infectious nidus could be used,
resuscitation after CLP in mice to imitate better the response to
1 wk, inducing chronic stress in the animal that well recapitulates
the environment in a typical ICU [58]. Other authors have
combined previous standard models, specifically T-H, followed by
polymicrobial sepsis to create a mouse acute lung injury/acute
respiratory distress model that attempts to recapitulate what
patients experience in the ICU; the incidence of sepsis after
trauma is substantial [6, 7, 44, 45, 59]. Researchers have created
a standardized, reproducible, and clinically relevant double-hit
mouse model induced by a focused blast wave to create chest
trauma, followed by polymicrobial sepsis [60]. Others have
further expanded immune research to include TBI by use of
a clinically relevant murine model that uses an impacting rod
directly on the skull [51]. However, even with all of these
efforts and novel methodologies, sepsis and trauma murine
research is still in a state of evolution and can be improved. For
example, researchers still need to work toward creating better
mouse pneumonia models for primary sepsis and sepsis
subsequent to trauma.

The value of these efforts rests with a realization that human
sepsis and trauma are much more complicated phenomena than
are engendered presently in our current animal models. What
remains unanswered is whether the presence of these funda-
mentally different transcriptional responses in mice, compared
with humans, can be overcome by simply making the models
more closely imitate the human disease—first raised by Seok
et al. [29] and addressed further by Efron and coworkers [32],
Osuchowski et al. [19], and Takao and Miyakawa [30]. Some
have concluded that even with murine models of trauma and
sepsis that more closely replicate the human condition, the
differences at the transcriptional level between the 2 mammals
are too great to put any reliance on the ability of murine models
for human medical research [29, 61, 62]. Unfortunately, there is
no easy answer to this question nor is there an easy approach to
address the challenge.

The other difficulty facing murine models of trauma or sepsis
is in replicating the timing of the host response. In addition to
improving the intensity of the rodent models, many investigators
have shifted their focus from the acute phase of trauma and
organs, as well as the systemic interaction of the individual as
a whole. Although hindsight is perfect, it should be of no surprise
that we have made only limited therapeutic progress in regards to
sepsis and trauma translational research; in the interest of
following appropriate scientific methodology (limiting the
number of variables), we have sacrificed our capacity to
reproduce the complexity of human inflammation appropriately.

Ask any ICU physician if there are a multitude of septic
middle-/high-school children in their ICUs. The answer will be "no." Yet, we study 6- to 12-wk-old mice. Ask which trauma
patients under the intensivist’s care have poor outcomes, and the
physician will tell you individuals with a combination of
prolonged hypovolemic shock, multiple severe compartmental
injuries, and blood product transfusion. Yet, accepted historical models of murine trauma only induce a transient period of
hemorrhagic shock, are not multicompartmental, and rarely
consider the effects of massive blood transfusion.

The improvement of murine models of sepsis and trauma is
neither a novel concept nor is there a single definitive solution.
When experiments moved from in vitro studies to animal models,
endotoxin challenge in young, healthy mice was obviously a first
effort. It has become increasingly clear that more complex and
pathologically relevant models, such as CLP in mice, or larger
animal hemodynamic models are probably more informative.
In fact, a step-wise approach to recapitulating the human condition
in rodents, while refraining from inhumane treatment, is the
keystone to our making progress in the field. Beginning more
than a decade ago, Daniel Remick and his colleagues [42, 43]
began promoting the use of antibiotics and crystalloid volume
resuscitation after CLP in mice to imitate better the response to
severe human infection; a greater infectious nidus could be used,
but the mouse could survive the acute phase of sepsis, as is typical
for human patients because of aggressive interventional support
(Table 2). As opposed to simple LPS injections, the pathologic
findings of apoptotic cell death of lymphocytes and gastrointestinal
epithelial cells that are one of the hallmarks of human sepsis
occur in the CLP animal model [39, 53, 54]. It should be noted,
though, that antibiotics and fluids only partly recreate the clinical
situation of humans in the ICU. Current models generally give
mice enough antibiotics to prolong survival but we are not able to
take the same curative approach as we do in humans. However,
gene expression studies of lymphocytes in septic mice and in
septic patients show very similar findings for the genes that
regulate cell death, further reinforcing the appropriateness of the
murine CLP model to study human sepsis [55].

Our group too realized that modifications were required in
our current murine models to make progress regarding trans-
lational research. Our laboratory examined large datasets, such
as the GG, to determine what modifications should be
implemented by examining those cohorts who had worse
outcomes with human severe trauma and apply those conditions
to our animal model [27, 28, 56]. Blood transfusion, age, and
injury severity are all significantly associated with worsened
outcomes in trauma (and sepsis for the former 2 characteristics)
[28, 33, 57]. Thus, we have examined blood transfusion in sepsis
[57] and aging as it relates to the innate-immune response in
sepsis and trauma [34, 41]. In addition, we have created a novel
PT model to reflect better the effects of hemorrhagic shock and
multicompartmental injury in humans [40]. In fact, this latter
murine model allowed us to expand subsequently on the
original Seok et al. [29] publication that failed to demonstrate
similar transcriptional regulation between human trauma and
an established murine trauma model. Specifically, we could
show that increasing the severity of the murine model resulted
in better correlations between the genome-wide murine and
human leukocyte transcriptomic response to trauma [32].
Although the overall improvement in that correlation was
modest, the inflammatory response between the 2 mammals
was remarkably similar at the level of the leukocyte tran-
scriptome [29, 32].

The expansion of the severity and resemblance of rodent
trauma and sepsis models to improve their similarity to the
human condition is not a unique approach to our laboratory. A
group from Rutgers-New Jersey Medical School has created a rat
model of combined hemorrhagic shock and pulmonary contu-
sion, an extremely common phenotype for patients in trauma
ICUs [58]. Even more, they subsequently performed intermittent
restraint and repositioning with alarms in the rodent for up to
1 wk, inducing chronic stress in the animal that well recapitulates
the environment in a typical ICU [58]. Other authors have
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sepsis to the chronic response. Acute death from sepsis and trauma is no longer the major cause of death in the ICU [13]. More commonly, we are finding patients surviving in the short term to go on to CCI and PICS [13]. Murine models have been notoriously poor at recapitulating CCI. Most existing trauma models study only the 1st 72–96 h after the response [40], and a 30% burn injury in the mouse will be healed completely by 14 d, where the host inflammatory response in patients with equivalent burns will last months and not days [63]. Several attempts have been made to create models of CCI. One such approach has been the sterile administration of zymosan, a fungal cell-wall product [48]. This produces a triphasic response associated with early mortality, a transient recovery period followed ultimately by death from multiple organ failure, 2–3 wk after induction [48]. Although on the surface, the timing and the phenotype of the inflammation recapitulate human CCI, a detailed investigation has revealed that the model is one of persistent hyperinflammation, without evidence of a simultaneous immune suppression, as is seen in humans with CCI and PICS [49]. Other approaches involve nonlethal peritonitis with a nidus of necrotic tissue created by a nonlethal CLP. We have shown that an LD$_{10}$ model of CLP produces a PICS-like syndrome in mice that demonstrates persistent inflammation and immunosuppression for up to 8 wk [64]. However, the model actually transitions from polymicrobial sepsis to the chronic response. Acute death from sepsis and trauma is no longer the major cause of death in the ICU [13]. More commonly, we are finding patients surviving in the short term to go on to CCI and PICS [13]. Murine models have been notoriously poor at recapitulating CCI. Most existing trauma models study only the 1st 72–96 h after the response [40], and a 30% burn injury in the mouse will be healed completely by 14 d, where the host inflammatory response in patients with equivalent burns will last months and not days [63]. Several attempts have been made to create models of CCI. One such approach has been the sterile administration of zymosan, a fungal cell-wall product [48]. This produces a triphasic response associated with early mortality, a transient recovery period followed ultimately by death from multiple organ failure, 2–3 wk after induction [48]. Although on the surface, the timing and the phenotype of the inflammation recapitulate human CCI, a detailed investigation has revealed that the model is one of persistent hyperinflammation, without evidence of a simultaneous immune suppression, as is seen in humans with CCI and PICS [49]. Other approaches involve nonlethal peritonitis with a nidus of necrotic tissue created by a nonlethal CLP. We have shown that an LD$_{10}$ model of CLP produces a PICS-like syndrome in mice that demonstrates persistent inflammation and immunosuppression for up to 8 wk [64]. However, the model actually transitions from polymicrobial sepsis to the chronic response. Acute death from sepsis and trauma is no longer the major cause of death in the ICU [13]. More commonly, we are finding patients surviving in the short term to go on to CCI and PICS [13]. Murine models have been notoriously poor at recapitulating CCI. Most existing trauma models study only the 1st 72–96 h after the response [40], and a 30% burn injury in the mouse will be healed completely by 14 d, where the host inflammatory response in patients with equivalent burns will last months and not days [63]. Several attempts have been made to create models of CCI. One such approach has been the sterile administration of zymosan, a fungal cell-wall product [48]. This produces a triphasic response associated with early mortality, a transient recovery period followed ultimately by death from multiple organ failure, 2–3 wk after induction [48]. Although on the surface, the timing and the phenotype of the inflammation recapitulate human CCI, a detailed investigation has revealed that the model is one of persistent hyperinflammation, without evidence of a simultaneous immune suppression, as is seen in humans with CCI and PICS [49]. Other approaches involve nonlethal peritonitis with a nidus of necrotic tissue created by a nonlethal CLP. We have shown that an LD$_{10}$ model of CLP produces a PICS-like syndrome in mice that demonstrates persistent inflammation and immunosuppression for up to 8 wk [64]. However, the model actually transitions from polymicrobial sepsis to the chronic response. Acute death from sepsis and trauma is no longer the major cause of death in the ICU [13]. More commonly, we are finding patients surviving in the short term to go on to CCI and PICS [13].
approach we have termed reverse translation (Fig. 1). This will involve not only determining a generalized medical problem in humans but also identifying a more specific phenotype or dysfunction in human patients before working with animal models. Subsequently, the investigators will have to “reverse translate” this work to the rodent—bedside to bench—confirming that the mouse model used indeed replicates the human condition at the mechanistic level and therefore, is a useful study approach. Only then can specific hypothesis-based work and interventions be performed, as required for drug development. Failure to demonstrate that the specific condition and hypothesis proposed in the mouse are mechanistically similar to humans will only lead to results that cannot be ultimately translated.

Although this is an oversimplified description of what would normally be a more complex pathway to human research, we anticipate that this will become the standard for future studies, requiring investigators to justify their animal model and mechanistic approach. Many models, such as the PT model, as well as the chronic restraint stress after injury and shock model, have already delineated this in their publications [32, 40, 49].

CONCLUDING REMARKS

In summary, current investigators must be willing to learn from the past to improve the future. Murine sepsis and trauma research is far from over, but it has to evolve. We are required to improve or adapt the well-established models of the past to increase their clinical relevancy and to demonstrate this scientific appropriateness to the audience/reviewers before implementation of vast rodent experimentation. It is only in this “future of murine sepsis and trauma research models” that we will be able to unravel the complexity of the human inflammatory response and identify modifications of the immune system that will improve the outcomes of the next generation of critically ill patients.

REFERENCES


DISCLOSURES

No conflict of, or competing, interests have been declared.

AUTHORSHIP

All authors contributed to writing the manuscript.

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